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(54) Title: MIXTURES OF ENANTIOMERS OF AMINOCYCLOHEXYLAMIDES TO PRODUCE SIMULTANEOUS ANALGESIA WITH LOCAL ANAESTHESIA OR ANTIARRHYTHMIA

(57) Abstract

The present invention provides compositions and methods for providing analgesia during the treatment of cardiac arrythmias or the induction of local anaesthesia. The compositions of the present invention include a plurality of vicinal aminocyclohexylamide enantiomers in ratios of stereo-specific configurations.

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MIXTURES OF ENANTIOMERS OF AMINOCYCLOHEXYLAMIDES TO PRODUCE SIMULTANEOUS ANALGESIA WITH LOCAL ANAESTHESIA OR ANTIARRHYTHMIA

TECHNICAL FIELD

The present invention relates generally to the use of mixtures of enantiomers of vicinal aminocyclohexylamides to produce local anaesthesia and/or antiarrhythmia, while at the same time producing an appropriate level of analgesia. This invention is more particularly related to the treatment of cardiac arrhythmias and the inducement of local anaesthesia, with an appropriate amount of analgesia.

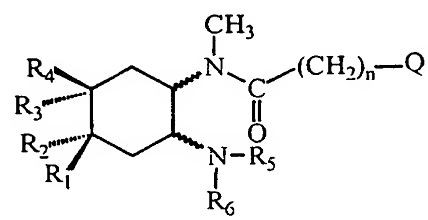
BACKGROUND OF THE INVENTION

Compounds are known that produce local anaesthesia and/or antiarrhythmic effects. It would be desirable to produce simultaneously an appropriate analgesic effect. Therefore, there is a need in the art to identify new compositions that produce the desired combination of effects. The present invention fulfills this need, and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for providing analgesia during the treatment of cardiac arrhythmias or the induction of local anaesthesia in a patient in need thereof. In one aspect, the present invention provides a composition comprising a plurality of vicinal aminocyclohexylamide enantiomers, wherein said composition of enantiomers is between about 85% to 99.99% R,R configuration and between about 15% to 0.01% S,S configuration. The compositions may optionally include a pharmaceutically acceptable carrier or diluent.

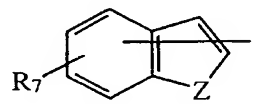
In an embodiment, the plurality of enantiomers are compounds of the formula:



(I)

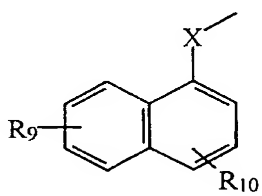
wherein n is either 0 or 1; R_1, R_2, R_3, R_4 are hydrogen, hydroxy, alkoxy of from one to four carbon atoms, or points of attachment of a spiro- or fused five- or six-membered heterocyclic ring containing one oxygen or sulfur atom;

R_5 and R_6 are either alkyl of from one to five carbon atoms or, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, morpholinyl, tetrahydroisoquinolinyl, or hexahydro-azepinyl ring; and Q is selected from the group of substituents comprising: 3,4,5-trimethylphenoxy;



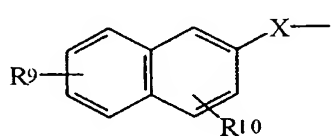
(II)

where R_7 is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl; Z is $-CH_2-$, -O-, -S-, or $N-R_8$ where R_8 is hydrogen, alkanoyl of from one to six carbon atoms, or alkyl of from one to six carbon atoms;



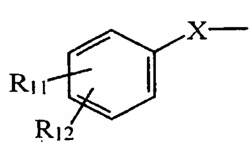
(III)

where X is CH_2, O or S, and R_9 and R_{10} are independently hydrogen, fluorine, bromine, alkyl of from one to six carbon atoms, or alkoxy of from one to four carbon atoms;



(IV)

where X and R_9 and R_{10} are defined as above; and



(V)

where X is defined as above, and R_{11} and R_{12} are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl.

In another aspect, the compositions of the present invention are provided for use as a medicament, and for use for the manufacture of a

medicament to provide analgesia during the treatment of cardiac arrhythmias or the induction of local anaesthesia. The present invention further provides for a method comprising the administration, to a patient in need of treatment for cardiac arrhythmias or the induction of local anaesthesia, of a composition according to the present invention.

These and other aspects of the present invention will become evident upon reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is directed toward mixtures of enantiomers of vicinal aminocyclohexylamides which have a variety of uses. Such uses include the inducement of local anaesthesia, treatment of arrhythmias and the blockade of ion channels *in vitro* and *in vivo*.

Aminocyclohexylamides are known in the literature and include those disclosed in U.S. Patent No. 5,506,257 and the patent and technical literature cited therein. As disclosed within the present invention, compositions that include mixtures of at least two enantiomers of vicinal aminocyclohexylamides produce, surprisingly, a combination of desirable effects.

Examples of vicinal aminocyclohexylamides include the class of substituted aminocyclohexylamide compounds depicted in formula I above. One nitrogen atom is an amine nitrogen substituted with R_5 and R_6 as defined above. Preferably, R_5 is methyl and R_6 is a lower alkyl, more preferably methyl, or, when taken together with the nitrogen atom to which they are attached, R_5 and R_6 preferably form a pyrrolidinyl ring, a morpholinyl ring or a hexahydroazepinyl ring. The other nitrogen atom is an N-methylamide substituted as described above, wherein n is preferably 1.

Preferably R_1, R_2, R_3 and R_4 are hydrogen or, R_3 and R_4 are hydrogen and R_1 and R_2 are an oxaspiran ring.

As used herein, the term "aryl" means phenyl; phenyl substituted with alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, nitro, or trifluromethyl; 2- or 3-thienyl; and, 2- or 3-thienyl substituted with alkyl of from one to four carbon atoms or alkoxy of from one to four carbon atoms.

In formula II depicted above, the bond that links the substituent with the remainder of the compound of formula I is shown as intersecting both rings of the fused ring structure of the substituent II. This indicates that the bond may be at any one of the carbon atoms in the fused ring structure except at position R_7.

Aminocyclohexylamides are depicted above in formula I by a structural formula. Such structural formula contains one or more asymmetric carbon atoms and therefore the compounds exist in various stereoisomeric

forms. In addition, the compound is capable of existing in different geometric isomeric forms. For example, the substituent R_1 of the cyclohexane ring may be positioned on the same side of the average plane of the ring as the amide nitrogen, or on the side opposite. In a preferred embodiment, the two nitrogens (amino and N-methylamide substituents) attached to the cyclohexyl ring are in a *trans* orientation. The present invention contemplates the use of geometric and stereoisomeric forms of the compounds of formula I.

Compounds of formula I may be used in the present invention as mixtures of individual enantiomers. Examples of individual enantiomers include compounds 2, 7 and 10 below. Examples of compounds that may be prepared as individual enantiomers, or prepared as racemic mixtures that are either separated into individual enantiomers or used as racemic mixtures, include the compounds listed below.

The following compounds and racemic mixtures are examples of compounds of formula I:

1. (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;
2. (1R,2R)-(+)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;
3. [(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
4. [(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide;
5. (±)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl) cyclohexyl](3,4-dichlorophenoxy)acetamide;
6. (±)-*trans*-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;
7. [5R-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;
8. (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide;
9. (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;
10. [5S-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;
11. (1S,2S)-(-)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
12. (1R,2R)-2-(indol-3-yl)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]acetamide;
13. (1S,2S)-2-(indol-3-yl)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]acetamide;

14. (1R,2R)-2-(2,3-dichlorophenoxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
15. (1S,2S)-2-(2,3-dichlorophenoxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
16. (1R,2R)-N-methyl-2-(1-naphthalenyloxy)-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
17. (1S,2S)-N-methyl-2-(1-naphthalenyloxy)-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
18. [1S-(1α,2β,4β)-N-methyl-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]furan-4-acetamide;
19. [1R-(1α,2β,4β)-N-methyl-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]furan-4-acetamide;
20. (1R,2R)-inden-2-yl-N-methyl-N-[2-(1,1-dimethylamino) cyclohexyl]carboxamide;
21. (1S,2S)-inden-2-yl-N-methyl-N-[2-(1,1-dimethylamino) cyclohexyl]carboxamide;
22. (1R,2R)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;
23. [(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
24. [(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide;
25. (1R,2R)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide;
26. (1S,2S)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;
27. [(1S,2S)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
28. [(1S,2S)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide; and
29. (1S,2S)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide.

The compounds of formula I may be prepared by known methods, including those described in the aforementioned United States patents to Horwell (all references cited in the present application, including those of Horwell, are incorporated herein in their entirety by reference). Suitable methods for the synthesis of diaminocyclohexane intermediates useful for preparation of a variety of compounds identified above are described in Szmuszkovicz, J., and Von Voightlander, P.F. (1982) *J. Med. Chem.*

25:1125-1126. The oxaspiro and methoxy-cyclohexanediamine intermediates useful for syntheses of compounds 7, 10, 18, and 19 are described in Halfpenny, P.R., et al. (1990) *J. Med. Chem.* *33*:286-291. Preparation or sources of the carboxylic acids used in the final stage of the syntheses of the compounds listed above are also to be found in the above references as well as in Clark, C.R., et al. (1988) *J. Med Chem.* *31*:831-836. The above latter three references contain information on all the steps of the syntheses of the compounds listed above, and provide sufficient guidance to a person skilled in the art to repeat the synthesis, isolation, and purification of these and many other analogous compounds. The individual enantiomers are obtained from mixtures of the different forms by known methods of resolution, such as the formation of diastereomers, followed by recrystallisation.

It will be appreciated by one of ordinary skill in the art that there are a variety of ways to produce the mixtures of the present invention. For example, the synthetic method for the compounds can be modified in order to obtain the desired mixture of enantiomers. For example, instead of using a single enantiomer of a chiral starting material, a prescribed ratio of enantiomers can be used in order to produce the desired mixture of enantiomers in the product. The conditions of synthesis can also affect the degree of enantiomeric purity for some compounds. A chiral compound can be synthesized as a pure enantiomer under certain conditions, but alteration of these conditions can result in some racemization. Taking advantage of this, a mixture of the present invention is made possible through such alteration of the conditions of chiral synthesis in order to produce the desired mixture of enantiomers in the product. Another procedure for obtaining the desired mixture of enantiomers entails the chiral synthesis of the two enantiomers, followed by admixture of the two enantiomers in the desired ratio. Another procedure for obtaining the desired mixture of enantiomers requires (a) chiral synthesis of the enantiomer that is required in the smaller quantity in the final mixture, (b) synthesis of the racemate, and (c) admixture of the racemate to the single enantiomer to give the desired final enantiomer ratio. Another procedure for obtaining the desired mixture of enantiomers is to separate a racemate solution using chiral separation techniques, such as preparative liquid chromatography with a chiral column, then mixing the enantiomers in the desired ratio.

The compounds of formula I may be in the form of a pharmaceutically acceptable acid addition salt. Such salts include the hydrochloride, sulfate, phosphate, citrate, and other salts known in the art. Pharmaceutical compositions of enantiomers of compound I or salts of compound I may contain pharmaceutically acceptable carriers or diluents, which are well known in the art.

Compositions of the present invention are prepared by mixing together two or more vicinal aminocyclohexylamide enantiomers. The aminocyclohexylamides may be vicinal at positions 1,2; 2,3; 3,4; 4,5; 5,6; 6,7; 7,8; etc.; depending on the rest of the structure of the compound as a whole. The resulting mixture yields compositions useful where analgesia is needed at the same time as local anaesthesia or antiarrhythmia. In a preferred embodiment, the aminocyclohexylamide enantiomers are present such that about 85%-99.99% are R,R configuration and about 15%-0.01% are S,S configuration. For example, an R,R enantiomer is present in a mixture at about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% (and numbers in between the integers) or up to 99.99%, with the remaining % as an S,S enantiomer. In a particularly preferred embodiment, about 99.5% are R,R and about 0.5% are S,S.

In order to assess whether a mixture has the required pharmacological activity within the present invention, it may be subjected to tests using methodology known in the art. For example, the antiarrhythmic activity of a compound may be estimated against the arrhythmias induced by coronary artery occlusion in anaesthetized rats. It is expected that a good antiarrhythmic compound will have antiarrhythmic activity at doses which have minimal effects on either the ECG, blood pressure or heart rate.

Similarly, a mixture may be assessed as an anaesthetic using a standard test for local anaesthetic effects. The following is a general description of such a test. Typically, a 20 microliter injection of the drug (or the carrier vehicle as a control) is made close to the base of the tail of a mouse. The needle is advanced until the tip contacts the caudal vertebra, then the solution is injected. After two minutes, the pin prick test is conducted both proximally and distally on either side of the injection site. If there is a tail flick response, a "Yes" is recorded. If there is no response, a "No" is recorded, indicating local anaesthesia.

Similarly, a mixture may be assessed as an analgesic using a standard test for analgesic effects. The following is a general description of such a test. Compounds over a range of doses (or vehicle control) are typically administered intravenously to mice weighing 20-30 g. At 5 and/or 15 minutes after injection a clip is placed at the base of the animal's tail and each animal is observed for a maximum period of 40 seconds; if the animal turns and bites the clip this indicates a lack of analgesia; whereas failure to turn and bite the clip indicates analgesia. The number of responders in each group is then determined and a dose which produces analgesia in 50% of animals (ED_{50}) is then calculated.

The mixtures of the present invention may be employed to treat the rhythm of a heart or prevent arrhythmias occurring in a heart that is susceptible to arrhythmia. Methods of administering effective amounts of

antiarrhythmic agents are well known in the art and include the administration of an oral or parenteral dosage form. Such dosage forms include, but are not limited to, parenteral solutions, tablets, capsules, sustained release implants, and transdermal delivery systems. Generally, oral or intravenous administration is preferred. The dosage amount and frequency is selected to create an effective level of the agent without harmful effects. It will generally range from a dosage of from about 0.1 to about 100 mg/kg/day, and typically from about 0.1 to 10 mg/kg where administered orally or intravenously for antiarrhythmic effect. For use as a local anaesthetic, a 0.1% to 1% solution injected into a local site is typical.

When the mixtures of the present invention are employed to induce local anaesthesia, the means of administration may be the same as described above in the case of treatment of arrhythmia, except that use of oral administration in the form of tablets or capsules will generally not be appropriate. Topical application of the local anaesthetic agent, for example in the form of an ointment or an aerosol spray, may be employed. Means of administering local anaesthetics are well known in the art.

Administration of the mixtures of this invention may be carried out in combination with the administration of other agents. For example, it may be desired to administer another antiarrhythmic agent or local anaesthetic.

The present invention also includes a commercial kit containing a pharmaceutical composition which includes two or more isomeric compounds of formula I or, pharmaceutically acceptable salts thereof, in addition to any desired, pharmaceutically acceptable, carriers or diluents. The commercial kit also includes instructions for the use of the pharmaceutical composition for the treatment of arrhythmia or for the inducement of local anaesthesia. Preferably the commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for the preparation of an intravenous injection. It will be evident to those in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

TRANS-N-METHYL-2-(1-PYRROLIDINYL)CYCLOHEXANAMINE

This compound was prepared based on the method in U.S. Patent No. 4,579,863.

(i) Cyclohexene oxide (202 mL, 2 mol) was added dropwise to aqueous methyl amine (466 mL or 40% solution, 6 mol) over 70 minutes. After a further 90 minutes, the temperature of the reaction mixture was 48°C and was reduced to 30°C by cooling in a water bath. After a further 2 hours, the mixture had returned to room temperature. It was stirred overnight, and then refluxed for 3 h. The mixture was saturated with sodium hydroxide (cooled during addition), extracted several times with diethyl ether (total 500 mL), the diethyl ether layer dried over sodium sulphate overnight, and the diethyl ether removed on a rotary evaporator. The remaining diethyl ether and cyclohexene oxide were removed by partial vacuum distillation. Distillation under full vacuum yielded a colorless fraction boiling at 95°C, (±)-*trans*-2-(methylamino)cyclohexanol: 217 g (84%).

(ii) A mixture of (±)-*trans*-2-(methylamino)cyclohexanol (200 g, 1.55 mol) and diethyl ether (400 mL) in a 3 L beaker was stirred and cooled in an ice bath as chlorosulfonic acid (103 mL, 1.55 mol) was added dropwise. After approximately 25 mL had been added, it was necessary to stir the thick mixture with a spatula, and after a further 40 mL of acid had been added more diethyl ether (200 mL) was added. The whole addition took 105 minutes. The sticky mixture was stirred by hand and left at room temperature for 2.5 hours. The mixture was filtered, and the solid washed with diethyl ether (300 mL). A solution of sodium hydroxide pellets (216 g) in water (1 L) was cooled in an ice bath, and then added slowly to the cooled solid. The mixture because less viscous and the addition was complete within 20 minutes. The mixture was left to stand overnight, then poured into a 2 L flask and steam distilled, with water being added from a dropping funnel to maintain constant volume in the distillation pot. After the diethyl ether had distilled, an organic product co-distilled with the water at a head temperature of 92-100°C (600 mL of a 2-phase colorless mixture was collected), to leave a small quantity of dark amber material on the surface of the water remaining in the distillation pot. The distillate was saturated with sodium hydroxide and extracted with diethyl ether (8 x 100 mL), the diethyl ether layer dried over sodium sulphate and the diethyl ether removed on a rotary evaporator to leave crude product (133 g) which was distilled under reduced pressure to give 7-methyl-7-azabicyclo[4.1.0]heptane (77.9 g, 43%).

(iii) A solution of ammonium chloride (1.6 g) in water (100 mL) was added to 7-methyl-7-azabicyclo[4.1.0]heptane (70 g, 0.59 mol) under nitrogen. Pyrrolidine (210 mL, 2.5 mol) was added and the mixture was stirred and refluxed under nitrogen for 20 hours. Sodium hydroxide was added to saturate the aqueous phase and the mixture was extracted with diethyl ether (7 x 100 mL). The combined organic extracts were washed with water (2 x 10 mL), and dried over sodium sulphate. The diethyl ether was removed on a rotary evaporator and excess pyrrolidine (60 mL) was distilled off under low vacuum. The product, (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]amine, was distilled under full vacuum (46-48°C). Yield 86 g (77%).

EXAMPLE 2

(±)-*TRANS*-N-METHYL-N-[2-(1-PYRROLIDINYL)CYCLOHEXYL]BENZO[B]THIOPHENE-4-ACETAMIDE MONOHYDROCHLORIDE

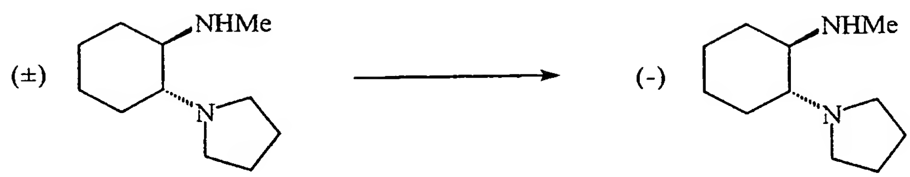
This compound was prepared according to the procedure described by C.R. Clark *et al.* in *J. Med. Chem. 31*:831-836, 1988. A solution of 4-thianaphtheneacetyl chloride (prepared by refluxing 4-thianaphtheneacetic acid (1.94 g, 10 mmol) with excess thionyl chloride) in dichloromethane (10 mL) was added dropwise to a solution of (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl] amine prepared in Example 1 (1.84 g, 10 mmol) in dichloromethane (10 mL) at 0°C. After stirring at room temperature for 10 minutes, diethyl ether was added until no further precipitate resulted. The crude product was collected by filtration, washed with diethyl ether and dried *in vacuo*. It was recrystallised from methanol/diethyl ether, to give the title compound, 3.3 g (85%). Proton and carbon-13 NMR data in accord.

Elemental analysis: Calcd. for $C_{21}H_{29}N_2OClS$: C 64.18, H 7.44%, N 7.13%; Found C 63.34, H 7.17, N 7.10.

EXAMPLE 3

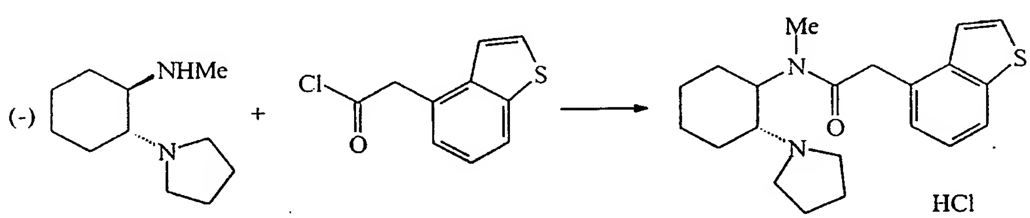
(1R, 2R)-(+)-*TRANS*-N-METHYL-N-[2-(1-PYRROLIDINYL)CYCLOHEXYL]BENZO[B]THIOPHENE-4-ACETAMIDE

A. <u>Resolution of (±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] amine</u>



The racemic diamine (Example 1) (16.0 g, 87.9 mmol) was dissolved in boiling methanol (400 mL). A solution of 2,3-di-*p*-toluoyl-D-tartaric acid (35.6 g, 92.1 mmol) in boiling methanol (400 mL) was added. A white precipitate formed immediately. The mixture was cooled to room temperature then the solid (40.4 g) was filtered off. This procedure was repeated twice more to obtain a total of 120 g of crude tartaric acid salt. The salt was washed with hot methanol (1 L) but the specific rotation of the free diamine was only -74 (lit. value: -96). Recrystallization from hot methanol in batches (5 g of salt in 600 mL MeOH) afforded 41.3 g of salt. The salt was partitioned between 20% KOH (600 mL) and CH_2Cl_2 (500 mL). The aqueous fraction was back-extracted with additional CH_2Cl_2 (4 x 100 mL). The CH_2Cl_2 extracts were combined and washed with distilled water (50 mL). The organic layer was dried by stirring it over anhydrous sodium sulphate. The solvent was removed *in vacuo* to yield the (-) diamine (13.5 g, 30%). Specific rotation: -93.

B. Synthesis of Title Compound



1. Acid chloride formation:

4-Thianaphtheneacetic acid (3.20 g, 17 mmol) was refluxed in thionyl chloride (18 mL) under nitrogen for 1 hour. After stirring at room temperature for an hour the thionyl chloride was removed *in vacuo* to leave a brown oil, which was dissolved in dichloromethane (18 mL).

2. Amide formation:

The acid chloride solution was added via cannula to a cooled solution of the (-) diamine (2.90 g, 16 mmol) in dichloromethane (15 mL).

The reaction was stirred at 0°C for 15 minutes and then stirred at room temperature for a further 45 minutes. Ether (40 mL) was added to the solution. An off-white solid precipitated from solution. The solid was filtered off and washed it with fresh ether (3 x 10 mL). The solid was recrystallized from hot methanol/ether (4.79 g, 77%). Specific rotation of the free acetamide (not the HCl salt):+29.3 (lit. value: +30).

EXAMPLE 4

ANTIARRHYTHMIA

Antiarrhythmic efficacy was assessed by investigating the activity of the compounds on the incidence of cardiac arrhythmias in pentobarbital anaesthetized rats subject to coronary artery occlusion. Arrhythmias were recorded as ventricular tachycardia (VT) and ventricular fibrillation (VF) and according to Curtis, M.J. and Walker, M.J.A. (1988) *Cardiovasc. Res. 22*:656. A detailed description of the antiarrhythmic activity of certain of the compounds used in the compositions of the present invention can be found in U.S. Patent No. 5,506,257 and the patent and technical literature cited therein.

Table 1 describes the result of tests of Compound 7 described therein as an ED_{50} value (which is the doses required to produce 50% reductions in the arrhythmic activity referred to therein). Initial results with compound 7 showed that at 2 and 8 μmol/kg, the incidents of fatal arrhythmias (VF) was reduced to 25% and 0%, respectively, from a control value of 88%.

Table 1

Activity	Compound 7
VT	8
VF	<1

Results of a more detailed study on the pharmacological and antiarrhythmic activities of Compound 7 (the R,R-enantiomer) and Compound 10 (the S,S-enantiomer) showed that both enantiomers (2 and 8 μmol/kg) equally reduced arrhythmias in anaesthetized rats subject to occlusion of a coronary artery as presented in Table 2 (Pugsley, M.K., et al. (1993) *British J. Pharm.* 1579-1585).

Table 2

Drug	Dose (μmol/kg)	Arrhythmia score
Saline	-	5.0±0.6
Compound 7	2	3.0±0.7
Compound 7	8	1.3±0.6*
Compound 10	2	1.1±0.6*
Compound 10	8	1.5±0.6*

Arrhythmia score according to Curtis, M.J. and Walker, M.J.A. (1988) *Cardiovasc. Res. 22*:656.

*P<0.05 for comparison with saline.

EXAMPLE 5

ANALGESIA

A compound or compounds over a range of dose (or vehicle control) were administered intravenously to mice weighing 20-30 g. At 5 and/or 15 minutes after injection a clip was placed at the base of the animal's tail and each animal observed for a maximum period of 40 seconds; if the animal turned and bit the clip this indicated a lack of analgesia: whereas failure to turn and bite the clip indicated analgesia. The number of responders in each group was then determined and a dose which produces analgesia in 50% of animals (ED_{50}) was then calculated.

A mixture of enantiomers of Compound 1 (racemic mixture) was compared to the individual enantiomer Compound 2. The Compound 1 mixture had an ED_{50} of 2 μmol/kg, whereas Compound 2 failed to produce analgesia at sub-lethal doses.

The analgesic activity of certain of the compounds used in the compositions of the present invention is described in Halfpenny, P.R., et al. (1990) *J. Med. Chem. 33*:286-291. It was determined that Compound 10 (the S,S-enantiomer) with a MPE_{50} (the dose required to produce 50% of the maximum possible analgesic effect using a rat paw pressure assay) value of 0.024 mg/kg is about 100 times more effective than Compound 7 (the R,R-enantiomer) with a MPE_{50} value of 2.5 mg/kg.

EXAMPLE 6

LOCAL ANAESTHESIA

A 20 microliter injection of the drug (or the carrier vehicle as a control) was made close to the base of the tail of a mouse. The needle was advanced until the tip contacts the caudal vertebra, then the solution was injected. After two minutes, the pin prick test was conducted both proximally and distally on either side of the injection site. If there was a tail flick response, a "Yes" was recorded. If there was no response, a "No" was recorded, indicating local anaesthesia.

Compound 2, tested at 0.05%, 0.1%, 0.2%, 0.4%, 1%, resulted in local anaesthesia in 0%, 33%, 60%, 100% and 100% of the mouse population, respectively. Saline injection failed to produce local anaesthesia. Lidocaine, as a positive control, at 0.1%, 0.5%, and 1%, produced local anaesthesia in 17%, 17% and 100% of the mouse population.

The local anaesthetic activity of certain of the compounds used in the compositions of the present invention is described in U.S. Patent No. 5,506,257.

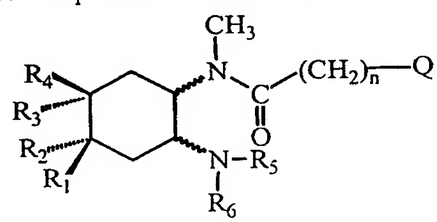
Compound 2 was evaluated for local anaesthetic effects in a Phase II human clinical trial. It was compared with lidocaine in a randomized, double-blind, placebo-controlled trial. Drugs at various concentrations (Compound 2: 0.05%, 0.15% and 0.25%; lidocaine: 0.2%, 0.6% and 1.0%) were injected intradermally in one of either forearms of 40 healthy male subjects. Local anaesthesia in the eight intradermal wheals (four wheals/forearm) was determined by a pin-prick score system and recorded at 1, 10, 30, 60 and 120 minutes post-injection. Solutions of Compound 2 were four times more potent than those of lidocaine in producing local anaesthesia with equal onset times at 10 minutes (mean pin prick score ± SEM at 10 minutes: Compound 2, 0.25%, 1.7±0.07; lidocaine, 1.0%, 1.73±0.07; P=NS). These results demonstrated that Compound 2 is a potent local anaesthetic in humans.

From the foregoing, it will be evident that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

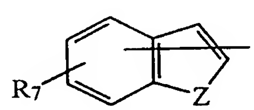
1. A composition comprising a plurality of vicinal aminocyclohexylamide enantiomers, wherein said composition of enantiomers is between about 85% to 99.99% R,R configuration and between about 15% to 0.01% S,S configuration, and optionally including a pharmaceutically acceptable carrier or diluent.

2. A composition according to claim 1, wherein the plurality of enantiomers are compounds of the formula:



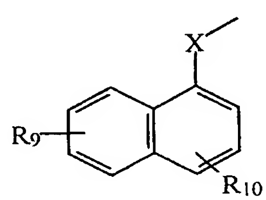
(I)

wherein n is either 0 or 1; R_1, R_2, R_3, R_4 are hydrogen, hydroxy, alkoxy of from one to four carbon atoms, or points of attachment of a spiro- or fused five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; R_5 and R_6 are either alkyl of from one to five carbon atoms or, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, morpholinyl, tetrahydroisoquinolinyl, or hexahydro-azepinyl ring; and Q is selected from the group of substituents comprising: 3,4,5-trimethylphenoxy;



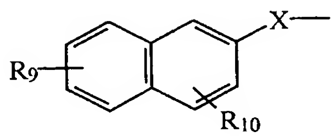
(II)

where R_7 is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl; Z is $-CH_2-$, -O-, -S-, or $N-R_8$ where R_8 is hydrogen, alkanoyl of from one to six carbon atoms, or alkyl of from one to six carbon atoms;



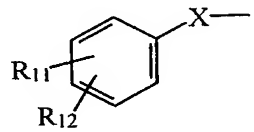
(III)

where X is CH_2, O or S, and R_9 and R_{10} are independently hydrogen, fluorine, bromine, alkyl of from one to six carbon atoms, or alkoxy of from one to four carbon atoms;



(IV)

where X and R_9 and R_{10} are defined as above; and



(V)

where X is defined as above, and R_{11} and R_{12} are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl.

3. A composition according to claim 2, wherein n=1; R_5 and R_6 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring; R_1, R_2, R_3 and R_4 are hydrogen; and Q is selected from the group comprising substituents II, III, and IV.

4. A composition according to claim 3, wherein Q is substituent II.

5. A composition according to claim 2, wherein n=1; R_5 and R_6 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring; R_3 and R_4 are hydrogen; R_1 and R_2 are selected from the group comprising hydrogen and points of attachment of an oxaspiran ring; and Q is selected from the group comprising substituents II, III and IV.

6. A composition according to claim 5, wherein Q is substituent II.

7. A composition according to claim 2, wherein an enantiomer is selected from the group consisting of the following compounds and racemic mixtures:

(±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;

(1R,2R)-(+)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;

[(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

[(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide;

(±)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl) cyclohexyl](3,4-dichlorophenoxy)acetamide;

(±)-*trans*-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;

[5R-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;

(±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide;

(±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;

[5S-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide;

(1S,2S)-(-)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

(1R,2R)-2-(indol-3-yl)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]acetamide;

(1S,2S)-2-(indol-3-yl)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]acetamide;

(1R,2R)-2-(2,3-dichlorophenoxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

(1S,2S)-2-(2,3-dichlorophenoxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

(1R,2R)-N-methyl-2-(1-naphthalenyloxy)-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

(1S,2S)-N-methyl-2-(1-naphthalenyloxy)-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

[1S-(1α,2β,4β)-N-methyl-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]furan-4-acetamide;

[1R-(1α,2β,4β)-N-methyl-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]furan-4-acetamide;

(1R,2R)-inden-2-yl-N-methyl-N-[2-(1,1-dimethylamino) cyclohexyl]carboxamide;

(1S,2S)-inden-2-yl-N-methyl-N-[2-(1,1-dimethylamino) cyclohexyl]carboxamide;

(1R,2R)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;

[(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

[(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide;

(1R,2R)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide;

(1S,2S)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide;

[(1S,2S)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

[(1S,2S)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide; and

(1S,2S)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide.

8. A composition according to claim 2, wherein an enantiomer is selected from the group consisting of the following compounds and racemic mixtures:

(±)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;

(1R,2R)-(+)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide;

[(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

[(±)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide; and

(±)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl) cyclohexyl](3,4-dichlorophenoxy)acetamide.

9. A composition according to claim 2, wherein an enantiomer is selected from the group consisting of:

[5S-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzo[b]furan-4-acetamide;

(1S,2S)-2-(benzo[b]thiophen-4-yl)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

(1R,2R)-2-(indol-3-yl)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]acetamide;

(1R,2R)-2-(2,3-dichlorophenoxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

(1R,2R)-N-methyl-2-(1-naphthalenyloxy)-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

[1S-(1α,2β,4β)-N-methyl-N-[4-methoxy-2-(1-pyrrolidinyl) cyclohexyl]benzo[b]furan-4-acetamide; and

(1R,2R)-inden-2-yl-N-methyl-N-[2-(1,1-dimethylamino) cyclohexyl]carboxamide.

10. A composition according to claim 2, wherein an enantiomer is:

(1R,2R)-*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-4-acetamide.

11. A composition according to claim 2, wherein an enantiomer is:

(1R,2R)-(+) -*trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzo[b]thiophene-3-acetamide.

12. A composition according to claim 2, wherein an enantiomer is:

[(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide.

13. A composition according to claim 2, wherein an enantiomer is:

[(1R,2R)-(1α,2β,4β,5β)]-N-methyl-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy) acetamide.

14. A composition according to claim 2, wherein an ènantiomer is:

(1R,2R)-*trans*-N-methyl-N-[2-(1-hexahydroazepinyl)cyclohexyl] (3,4-dichlorophenoxy)acetamide.

15. A composition according to claim 2, wherein an enantiomer is:

[5R-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide.

16. A composition according to claim 2, wherein an enantiomer is:

[5S-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[b]furan-4-acetamide.

17. A method for providing analgesia during the treatment of cardiac arrhythmias or the induction of local anaesthesia in a patient in need thereof, comprising administering to said patient an effective amount of a composition according to claim 1.

18. The method of claim 17, wherein the composition is according to any one of claims 2-16.

19. A composition according to any one of claims 1-16 for use as a medicament.

20. Use of a composition according to any one of claims 1-16 for the manufacture of a medicament to provide analgesia during the treatment of cardiac arrhythmias or the induction of local anaesthesia.

INTERNATIONAL SEARCH REPORT

Inter. nı pllcation No
PCT/CA 98/00905

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/16 A61K31/40 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 506 257 A (MACLEOD ET AL) 9 April 1996 cited in the application see the whole document	1-8
A	US 4 212 878 A (LEDNICER ET AL.) 15 July 1980	
A	EP 0 110 869 A (LAEVOSAN GMBH) 13 June 1984	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 1999	01/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klaver, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5506257 A	09-04-1996	AT 154934 T	15-07-1997
		AU 3882793 A	21-10-1993
		CA 2132841 A	30-09-1993
		WO 9319056 A	30-09-1993
		DE 69311896 D	07-08-1997
		DE 69311896 T	16-10-1997
		EP 0632806 A	11-01-1995
		ES 2104142 T	01-10-1997
		JP 7505151 T	08-06-1995
US 4212878 A	15-07-1980	NONE	
EP 110869 A	13-06-1984	AT 376669 B	27-12-1984
		AT 430882 A	15-05-1984
		CA 1244438 A	08-11-1988
		CS 9103322 A	15-04-1992
		DK 540283 A,B,	27-05-1984
		FI 834323 A,B,	27-05-1984
		JP 1819503 C	27-01-1994
		JP 5027634 B	21-04-1993
		JP 59106484 A	20-06-1984
		PT 77745 B	16-04-1986
		US 4499286 A	12-02-1985